

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 09 January 2001 (09.01.01)	
International application No. PCT/GB00/01521	Applicant's or agent's file reference KR/P32286
International filing date (day/month/year) 19 April 2000 (19.04.00)	Priority date (day/month/year) 20 April 1999 (20.04.99)
Applicant BLACKLER, Paul, David, James et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

14 November 2000 (14.11.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference DF/KR/P32286		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01521	International filing date (day/month/year) 19/04/2000	Priority date (day/month/year) 20/04/1999	
International Patent Classification (IPC) or national classification and IPC C07D417/00			
Applicant SMITHKLINE BEECHAM P.L.C. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 14/11/2000		Date of completion of this report 30.05.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Fritz, M Telephone No. +49 89 2399 2792	



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01521

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-9 as originally filed

Claims, No.:

1-12 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01521

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 12.

because:

☒ the said international application, or the said claims Nos. with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims 1-11

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01521

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 12 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: CANTELLO B C C ET AL: 'Facile biocatalytic reduction of the carbon-carbon double bond of 5-benzylidenethiazolidine-2,4-diones. Synthesis of (+,-)-5-(4-{2-[methyl(2-pyridylamino) ethoxy]benzyl}thiazolidine-2,4 -dione (BRL49653), its (R)-(+)-enantiomer and analogues' JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1994, pages 3319-3324-3322, XP002099539 ISSN: 0300-922X
- D2: WO 94 05659 A (SMITHKLINE BEECHAM PLC) 17 March 1994 (1994-03-17) cited in the application

The present application relates to the hydrochloride dihydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (claims 1-6), a process for preparing this hydrate (claim 7), pharmaceutical compositions thereof (claim 8), a hydrate according to claim 1 for the use as a therapeutically active substance (claim 9) and for use in the treatment of diabetes mellitus (claim 10), the usage thereof for the manufacture of a medicament (claim 11) as well as a method of treatment by administering the hydrate according to claim 1 (claim 12)

For the assessment of the present claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can al-

so be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Racemic 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione and its R-(+)-enantiomer are described in D1. D1 furthermore teaches that the treatment of R-(+)-5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione with concentrated hydrochloric acid leads to the **monohydrate** hydrochloride salt thereof (cf. D1, p. 3323, right-hand column, synthesis of compound 6).

Example 1 of D2 describes the maleate salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione comprising also residual water. In D2 (p. 1, lines 24-25) it is emphasized that the salts of the compounds I (of which 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione is a representative) are characterized by significant formulation and bulk handling advantages. Among the favoured pharmaceutically acceptable acids hydrochloric acid is mentioned (D2, p. 2, lines 12-14).

Therefore the subject-matter of claims 1 - 11 according to the present application is novel in the sense of Article 33(2) PCT.

The problem of the present application was to provide 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione in a form which is particularly suitable for bulk preparation.

Closest prior art is D2.

As D2 refers to significant formulation and bulk handling advantages of pharmaceutically acceptable salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (which was demonstrated in ex. 1 and also ex. 2 of D2), the person skilled in the art only had to choose HCl as pharmaceutically acceptable acid in order to solve the problem underlying the present case.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/01521

Since hydrochloric acid is even suggested as favourable pharmaceutically acceptable acid, (see above) this selection must be considered an obvious solution of the problem.

By consequence an inventive step in the sense of Article 33(3) PCT cannot be acknowledged for the subject-matter of claims 1-11 according to the present case, as the applicant has not demonstrated an unexpected effect distinguishing the hydrochloride dihydrate according to the present case further from the maleate salt described in D2.

Re Item VIII

Certain observations on the international application

Obviously claim 11 (and also 12) refer to the hydrate according to claim 1. This should be indicated in order to fulfill the requirements set forth in Article 6 PCT.

The terms "substantially" (claims 2, 3), "isolated" (claim 4), "pure" (claim 5) as well as "certain complications" (claims 10-11) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Claims 2 and 3 contain a reference to the drawings.

According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

It is noted that the subject-matter of the present case is identical with that of the International Application No. PCT/GB00/01527.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 October 2000 (26.10.2000)

PCT

(10) International Publication Number
WO 00/63205 A3

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- (21) International Application Number: PCT/GB00/01521
- (22) International Filing Date: 19 April 2000 (19.04.2000)
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- (26) Publication Language: English
- (30) Priority Data: 9909041.7 ✓ 20 April 1999 (20.04.1999) GB
- (71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): BLACKLER, Paul, David, James [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). GILES, Robert, Gordon [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). SASSE, Michael, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB).
- (54) Title: THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC
- (57) Abstract: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate characterised in that it: (i) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 cm⁻¹; and/or (ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.
- (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).
- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (88) Date of publication of the international search report: 25 January 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 00/63205 A3

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/12 A61K31/427 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CANTELO B C C ET AL: "Facile biocatalytic reduction of the carbon-carbon double bond of 5-benzylidenethiazolidine-2,4-diones. Synthesis of (+,-)-5-(4-[2-(methyl(2-pyridylamino)ethoxy)benzyl]thiazolidine-2,4-dione (BRL49653), its (R)-(+)-enantiomer and analogues"</p> <p>JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1994, pages 3319-3324-3322, XP002099539 ISSN: 0300-922X</p> <p>the whole document, particularly page 3321, left-hand column, first text-paragraph, penultimate sentence, and page 3323, right-hand column, preparation of compound 6</p> <p style="text-align: center;">— — — — — -/-</p>	1,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

2 August 2000

Date of mailing of the international search report

16/08/2000

Name and mailing address of the ISA

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Authorized officer

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11, 12 (both partly)

Contrary to the requirements of Article 6 PCT, claims 11 and 12 do not clearly define the matter for which protection is sought. The search with regard to these claims has therefore been limited to the use of a hydrate as defined in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 00/01521

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 05659 A (SMITHKLINE BEECHAM PLC) 17 March 1994 (1994-03-17) cited in the application the whole document, particularly page 2, lines 12-14	1,8
A	HALEBLIAN J ET AL: "Pharmaceutical application of polymorphism" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 58, no. 8, 1 August 1969 (1969-08-01), pages 911-929, XP002020518 ISSN: 0022-3549 the whole document	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Initial Application No

PCT/GB 00/01521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405659 A	17-03-1994	AT 182147 T	15-07-1999
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